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A [3+2] NITRILE OXIDE INTERMOLECULAR CYCLOADDITION APPROACH TO 4,5-DIHYDRO-3(2H)-FURANONE AND 3(2H)-FURANONE RING SYSTEMS: APPLICATION TO THE FORMAL SYNTHESIS OF (±)-ASCOFURANONE AND GEIPARVARIN.

M. Aghazade Tabrizi, P.G. Baraldi, M. Guarneri, S. Manfredini, G.P. Pollini and D. Simoni*

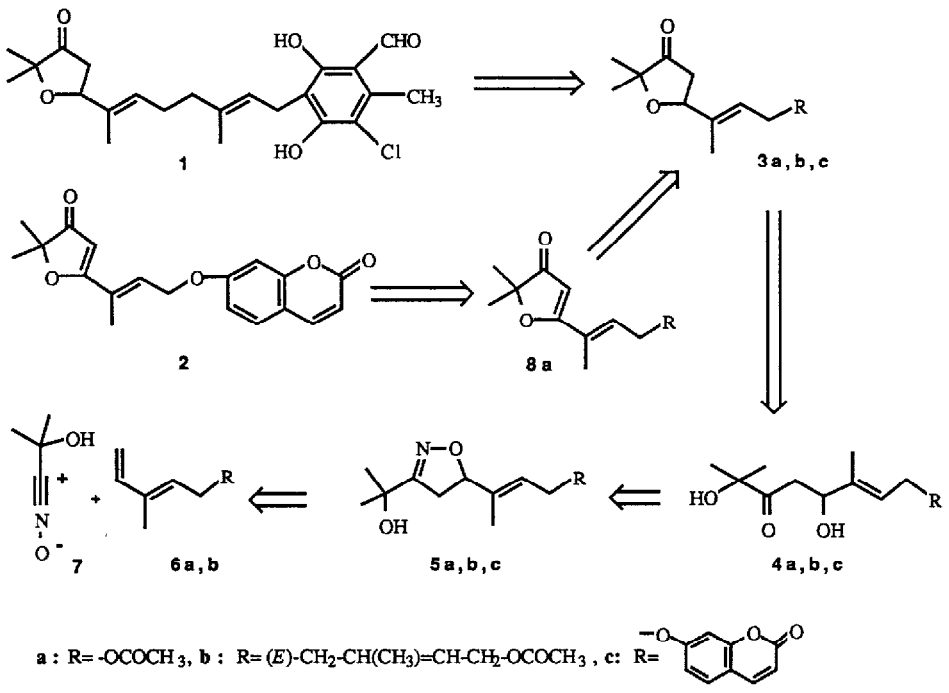
Dipartimento di Scienze Farmaceutiche , Università di Ferrara , Via Scandiana 21. I-44100 Ferrara

Summary. A unified approach to both 4,5-dihydro-3(2H)-furanone and 3(2H)-furanone ring systems centered on a [3+2] nitrile oxide cycloaddition strategy as a tool for the crucial carbon-carbon bond forming step has been successfully applied to the formal synthesis of (±)-ascofuranone and to a new synthesis of geiparvarin from common intermediates.

A wide range of biological properties are associated with an increasing number of natural compounds incorporating 3(2H)-furanone and 4,5-dihydro-3(2H)-furanone ring systems as common structural feature[1,2]. These uncommon systems with extensive functionalizations continue to present formidable synthetic challenge to the organic chemist despite the advances made during the past decade. Consequently considerable efforts have been made in this direction and a number of different approaches have appeared in the recent literature[3,4].

As a part of a synthetic program centered on the development and the execution of [3+2] nitrile oxide cycloaddition strategies for the construction of natural products[5], we were intrigued in applying this chemistry to a convenient preparation of the 4,5-dihydro-3(2H)-furanones **3a,b**, two immediate precursors of (±)-ascofuranone **1**. Moreover the flexibility of our approach is further illustrated by the conversion of **3a** to suitable 3(2H)-furanone **8a** as required for the synthesis of geiparvarin **2**. The overall synthetic plan is retrosynthetically depicted in the Scheme. Thus the preparation of the isoxazolines **5a,b*** called for a regio- and chemoselective cycloaddition of the nitrile oxide **7**, generated from the corresponding primary nitro compound under Mukaiyama conditions[6], and the dienes **6a,b** possessing the required *E*-geometry of the double bonds in the appropriate position as in the target **1**.

Scheme

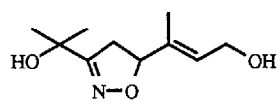


The reductive N-O cleavage[7] of the isoxazoline **5a** with $Mo(CO)_6$ in wet acetonitrile afforded the α',β-dihydroxyketone **4a** in 50% yield, whereas ring cleavage of the isoxazoline **5b**, employing the method described by Guarna et. al.[8], gave a 4:1 mixture of α',β-dihydroxyketone **4b** together with the derived α,β-unsaturated ketone in 50% overall yield. Cyclization of **4a,b** was eventually promoted by treatment with p-TsOH in 2-methoxy-1,3-dioxolane containing a small amount of MeOH providing a 45% yield of the known **3a,b****, which have been already taken to (±)–ascofuranone[1,2].

Interestingly oxidation of **3a** by simple heating in dioxane with dichloro-dicyano-benzoquinone (DDQ) resulted in its quantitative conversion to the 3(2H)-furanone **8a**, a well established[3] precursor of geiparvarin **2**.

As a further demonstration of the versatility of the cycloadditive strategy for the preparation of both 4,5-dihydro- and 3(2H)-furanone ring systems, we have

developed an alternative approach to the synthesis of geiparvarin **2** starting from the above described isoxazoline **5a**. Lithium hydroxide saponification, followed by condensation of the derived allylic alcohol **9** with 7-hydroxycoumarin in the presence of diethyl azodicarboxylate and triphenylphosphine, afforded the intermediate **5c** incorporating the complete carbon atom framework of the natural target. Its exposure to $Mo(CO)_6$, utilizing the same procedure described for **5b**, followed by cyclization of the derived α',β-dihydroxyketone **4c** with p-TsOH in 2-methoxy-1,3-dioxolane containing a small amount of MeOH led to the formation of the 4,5-dihydro-3(2H)-furanone **3c** in 30% overall yield. The remaining transformation, namely DDQ oxidation as described for **8a** proceeded without incident to provide synthetic **2**, identical in all respects with an authentic sample of geiparvarin.



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In summary we have devised a method for the synthesis of both 3(2H)-furanone and its dihydro derivative ring systems employing common intermediates, which are in turn easily available through elaboration of the heterocycles resulting from [3+2] nitrile oxide-olefin cycloaddition methodology in the classical intermolecular version.

Acknowledgments. Thanks are due to Consiglio Nazionale delle Ricerche (Roma) for financial support.

References and Notes.

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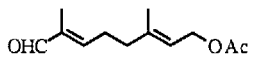
* All compounds gave spectral and analytical data consistent with the assigned structures. Compounds **5a,b** were obtained in 75% and 70% yields respectively by silica gel column cromatography of the crude cycloadducts isolated by standard work-up.
The required nitro compound was the easily available Henry adduct between acetone and nitromethane Diene **6a** was prepared by partial hydrogenation of the commercially available (*E*)-3-methyl-2-penten-4-yn-1-ol, while **6b** was produced in 60% yield by Wittig methylenation of the aldehyde **i**, in turn secured by SeO_2 mediated stereoselective oxidation of geranyl acetate: K. Mori, M. Ohkiand and M. Matsui, Tetrahedron, 1974, **30**, 715



i

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** Selected spectral data are given. All ^1H NMR spectra were recorded on Bruker AC 200 spectrometer in $CDCl_3$.
4a, oil; IR (neat): 3400, 1740, 1715 cm^{-1}; ^1H NMR: δ 1.36 (s, 6H), 1.73 (s, 3H), 2.06 (s, 3H), 2.70, 2.91 (2H, ABX System J= 16.5, 3.1, 9 5 Hz), 3.24 (s, 1H), 3.86 (s, 1H), 4.51 (m, 1H), 4 65 (d, 2H , J= 6.3 Hz), 5.66 (brt, 1H).
4b, oil; IR (neat): 3400, 1740, 1715 cm^{-1}; ^1H NMR: δ 1.36 (s, 6H),1.62 (s, 3H), 1.69 (s, 3H), 2.04 (s, 3H), 1.95-2.17 (m, 4H), 2.63, 2.93 (2H, ABX System J= 16.4, 3.0, 9.4 Hz), 3.5 (br, 2H), 4.46 (m, 1H), 4.58 (d, 2H, J= 6.2 Hz), 5.32 (brt, 1H), 5.43 (brt, 1H).
4c, oil; IR (neat): 3400, 1740-1700, 1620, 1550, 1500 cm^{-1}; ^1H NMR: δ 1.51 (s, 6H), 1.75 (s, 3H), 2.42 (s, 1H), 2.95, 3.24 (2H, ABX System J= 17.2, 8.3, 11.0 Hz), 3.64 (s, 1H), 4.65 (d, 2H, J= 6.1 Hz), 5.1 (m, 1H), 5.79 (brt, 1H), 6.24 (d, 1H, J=9.4 Hz), 6.84 (m, 2H); 7.38 (d, 1H, J= 8.3 Hz), 7.65 (d, 1H, J= 9.4 Hz).
3a, oil; IR (neat): 1760, 1740, 1665 cm^{-1}; ^1H NMR: δ 1.24 (s, 3H); 1.32 (s, 3H), 1.75 (s, 3H), 2.06 (s, 3H), 2.43, 2.59 (2H, ABX System J= 18.0, 10.1, 6.2 Hz), 4.58 (m, 1H), 4.67 (d, 2H, J= 6.3 Hz), 5.77 (brt, 1H).
3c, m.p. 114-116°C (Ethyl Acetate-Petroleum Ether); IR ($CHCl_3$): 1760, 1735, 1620, 1560, 1510 cm^{-1}; ^1H NMR: δ 1.25 (s, 3H), 1.33 (s, 3H), 1.81 (s, 3H), 2 45, 2.62 (2H, ABX System J= 18.1, 10.1, 6.1 Hz); 4.60 (m, 1H), 4.68 (d, 2H, J= 6.2 Hz), 5.91 (brt, 1H), 6.26 (d, 1H, J= 9.4 Hz), 6.86 (m, 2H), 7.38 (d, 1H, J= 8.4 Hz), 7.65 (d, 1H, J= 9.4 Hz).

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